have been included in Claim 1. Correspondingly, Claim 4 has been amended to depend upon Claim 1 instead of Claim 3. Further, applicants have added new Claims 16 to 25 to bring out some of the embodiments of the rate-controlled release particles of Claim 1. New Claims 16, 17, 19, 21 and 22 further characterize the surfactant which is present in the particles in accordance with the disclosure on page 12, indicated lines 28 to 38, of the application, and new Claim 18 further specifies the amount of the N-vinylpyrrolidone homo- or copolymer of the particles defined in Claim 16 corresponding to the provisions of Claim 7. New Claim 20 additionally requires that the particles consist essentially of the active ingredient, the homo- or copolymer, the surfactant and, optionally, citric acid and/or hydroxypropyl methyl cellulose, and that the requisite constituents be present in the amounts set forth on page 12, indicated lines 24 to 26, and indicated lines 37 to 45, of the application. New Claims 23 to 25 further require the particles defined in Claims 1, 16 and 20 to be obtained by a melt extrusion process as addressed on page 13, indicated lines 8 to 11, of the application. No new matter has been added.

The Examiner rejected Claims 1 to 4 and 6 to 15 under 35 U.S.C. §103(a) as being unpatentable in light of the teaching of ***Andries et al.*** **(US 6,197,779)** when considered in view of the disclosures of ***Goertz et al.*** **(US 4,801,460)**, of ***Nakamichi et al.*** **(US 5,456,923)**, of ***Sasatani et al.*** **(US 5,876,760)**, and of ***Takada*** **(US 5,350,741)**. In light of the following, the Examiner's reasons for rejecting applicants' claims are not deemed to apply where the claims which are herewith presented by applicants are concerned.

Claim 1 as herewith presented as well as the dependent claims relate to rate-controlled release particles which

(1) comprise

- a compound as represented by applicants' formulae (I) to (VI) as an active ingredient,
- a polymer matrix consisting of a homo- or copolymer of N-vinylpyrrolidone, and
- a surfactant; and

(2) comprise the active ingredient as a solid dispersion in the polymer matrix.

The teaching of ***Andries et al.*** merely provides that active ingredi-

ents within applicants' definition are known in the art and can be applied in various conventional dosage forms. Accordingly, the teaching of ***Andries et al.*** differs from applicants' invention not only because ***Andries et al.*** fail to expressly teach a dosage form in which PVP is a carrier and a surfactant and/or citric acid is used as an additional excipient or the release forms as summarized by the Examiner. The teaching of ***Andries et al.*** differs from applicants' invention also because ***Andries et al.*** fail to teach a dosage form in which the active ingredient is present in form of a solid dispersion in a polymer matrix consisting of homo- or copolymers of N-vinylpyrrolidone in combination with a surfactant.

The Examiner applied the disclosures of ***Goertz et al.*** and of ***Nakamichi et al.*** for showing solid pharmaceutical dosage forms which comprise an active ingredient in form of a solid solution or dispersion in a binder polymer such as homo- or copolymers of N-vinylpyrrolidone. However, even when these references are considered along with the teaching of ***Andries et al.*** a person of ordinary skill in the art would not reasonably arrive at the particular combination of requirements which characterizes applicants' invention.

The disclosure of ***Goertz et al.*** relates to pharmaceutical dosage forms in which the pharmaceutical ingredient is present in form of a solid solution or dispersion in a tolerable fusable binder wherein the fusible binder is an NVP polymer which contains no less than 20% by weight of NVP as copolymerized units[2] which optionally further comprise plasticizers[3] and other conventional auxiliaries[4]. Other conventional auxiliaries which are suitable for application in such dosage forms are, according to the disclosure of ***Goertz et al.***, extenders, wetting agents, preservatives, disintegrating agents, absorbents, colorants and flavorings[5]. The disclosure of ***Goertz et al.*** therefore fails to suggest to a person of ordinary skill in the art to employ a surfactant in a dosage form wherein a pharmaceutical ingredient is present in form of a solid solution or dispersion in an N-Vinylpyrrolidone homo- or copolymer binder matrix.

The disclosure of ***Nakamichi et al.*** primarily relates to an improved process for producing solid dispersions of pharmaceutical in-

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2) Cf. col. 1, indicated line 64, to col. 2, indicated line 16, of ***US 4,801,460***.

3) Cf. col. 2, indicated lines 30 to 49, of ***US 4,801,460***.

4) Cf. col. 1, indicated line 68, to col. 2, indicated line 1, and col. 5, indicated lines 3 to 6, of ***US 4,801,460***.

5) Cf. col. 5, indicated lines 38 to 48, of ***US 4,801,460***.

gredients[6] wherein the improvement is achieved by using a particular twin-screw extruder[7]. As such, the disclosure of ***Nakamichi et al.*** does not particularly address the constituents of a particle comprising the pharmaceutical and the polymeric binder. In fact, ***Nakamichi et al.*** merely mention and illustrate the addition of plasticizers[8] and illustrate the inclusion of extenders[9]. The disclosure of ***Nakamichi et al.*** is therefore also not suitable to motivate a person of ordinary skill in the art to incorporate a surfactant, and optionally citric acid and/or hydroxypropyl methyl cellulose, into a dosage form which contains a pharmaceutical ingredient in form of a solid solution or dispersion in a binder matrix consisting of an N-Vinylpyrrolidone homo- or copolymer.

The Examiner applied the disclosures of ***Sasatani et al.*** and of ***Takada*** for showing solid pharmaceutical dosage forms which comprise an active ingredient, a polymer and a surfactant as well as optionally citric acid. However, these references relate to dosage forms which are obtained by dissolving or dispersing the constituents of the dosage forms and subsequently evaporating the solvent(s) to obtain the particles[10]. The surfactant is, accordingly, not employed for the benefit of the dosage form but rather serves to provide for a solution or dispersion of the constituents which is suitable for the spray-drying procedure[11]. Moreover, ***Takada*** specifically points out that the resulting dosage form is not a solid solution or dispersion of the active ingredient in the polymer matrix stating[12]

> *The differences of the present invention from applications (1) to (5) described above reside in the following points. In application (1), a drug is dispersed on a molecular level in a water-soluble polymer matrix; on the other hand, in the present invention* the drug exists in the state of solid crystals *coated with a saccharide.*

In addition to those pertinent distinctions between the dosage forms

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6) Cf. col. 1, indicated lines 54 to 57, of ***US 5,456,923***.

7) Cf. col. 1, indicated lines 58 to 61, of ***US 5,456,923***.

8) Cf. col. 3, indicated lines 28 to 44, and Examples 1 to 3, 5, 8 and 9, of ***US 5,456,923***.

9) Cf. Examples 4 and 5, col. 7, indicated lines 13 to 39, of ***US 5,456,923***.

10) Cf. for example col. 2, indicated lines 44 to 48, of ***US 4,876,760***, and col. 2, indicated lines 54 to 60, of ***US 5,350,741***.

11) Cf. col. 2, indicated lines 54 to 60, of ***US 5,350,741***, and col. 4, indicated lines 39 to 45, of ***US 5,876,760***.

12) Cf. col. 4, indicated lines 24 to 29, of ***US 5,876,760***.

addressed by ***Sasatani et al.*** and ***Takada*** on the one hand, and the solid solution preparations which are addressed in the disclosures of by ***Goertz et al.*** and of ***Nakamichi et al.*** on the other hand, it is also noted that both ***Sasatani et al.*** and ***Takada*** deal with pharmaceutical ingredients which are structurally as well as physiologically distinctly different from the active ingredients which are present in applicants' rate-controlled release particles. The disclosure of ***Sasatani et al.*** is concerned with spray-dried granules of pranlucast and more particularly with solving adhesiveness problems which are particular to the processing of that specific drug. A person of ordinary skill in the art developing a solid solution dosage form for an active ingredient which is distinctly different from pranlucast would not reasonably consider the teaching of ***Sasatani et al.*** as analogous art[13]:

- the disclosure of ***Sasatani et al.*** is not in the field of solid solution dosage forms of pharmaceutical ingredients corresponding to applicants' active ingredients (I) to (VI); rather, it relates to a dosage form which is expressly different from solid solution dosage forms and which comprises a distinctly different pharmaceutical ingredient;
- the disclosure of ***Sasatani et al.*** is not pertinent to the problem of finding rate-controlled solid solution dosage forms for pharmaceutical ingredients corresponding to applicants' active ingredients (I) to (VI).

Essentially the same applies where the disclosure of ***Takada*** is concerned since ***Takada***, like ***Sasatani et al.***, refer to spray-died preparations which comprise a proteinous drug as the active ingredient, that is, a drug which is distinctly different from the active ingredients which are required in accordance with applicants' invention. A combination of references is improper if one of the references is non-analogous art[14], and if a cited reference is not analogous art, it has no bearing on the obviousness of the claim[15]. The Examiner's reliance upon the disclosures of ***Sasatani et al.*** and of ***Takada*** in the rejection of applicants' claims under Section 103(a) is, therefore, deemed to be in error.

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13) Cf. In re Clay, 966 F.2d 656, 23 USPQ2d 1058 (CAFC 1992).

14) In re Clay, ibid.

15) Cf. Jurgens v. McKasy, 927 F.2d 1552, 18 USPQ2d 1031 (CAFC 1991), *cert. denied*, 502 U.S. 902 (1991).

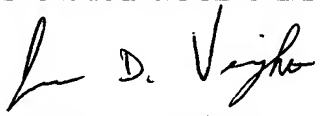
In light of the foregoing, the Examiner's position that applicants' invention is rendered prima facie obvious within the meaning of Section 103(a) by the teaching of ***Andries et al.*** when taken in view of the disclosures of the referenced secondary art is not deemed to be well taken. Favorable reconsideration of the Examiner's position and withdrawal of the respective rejection is, therefore, respectfully solicited.

REQUEST FOR EXTENSION OF TIME:

It is respectfully requested that a *one* month extension of time be granted in this case. The respective *$120.00* fee is paid by credit card (Form PTO-2038 enclosed).

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees, to Deposit Account No. 14.1437. Please credit any excess fees to such deposit account.

Respectfully submitted,
NOVAK DRUCE DELUCA & QUIGG



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Encl.: CLAIM AMENDMENTS (Appendix II)

JDV/BAS

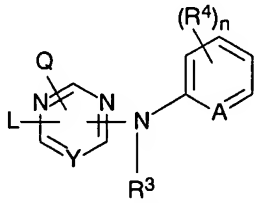
APPENDIX I:

CLAIM AMENDMENTS:

Cancel Claim 3, amend Claims 1 and 4, and enter new Claims 16 to 25 as indicated in the following listing of the claims:

1. (*currently amended*) Rate-controlled release particles, comprising an active ingredient as a solid dispersion in a polymeric matrix consisting of a homo- or copolymer of N-vinylpyrrolidone and further comprising a surfactant, and wherein the active ingredient is

a compound of formula I



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

Y is CR^5 or N;

A is CH, CR^4 or N;

n is 0, 1, 2, 3 or 4;

Q is $-NR^1R^2$ or when Y is CR^5 then Q may also be hydrogen;

R^1 and R^2 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl

wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxy-C_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imido, aminocarbonyl, aminocarbonylamino, mono- or di(C_{1-6}alkyl)amino, aryl and Het; or

R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}-alkylidene;

R^3 is hydrogen, aryl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxycarbonyl; and

each R^4 independently is hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalome-

thyloxy, or when Y is CR^5 then R^4 may also represent C_{1-6}alkyl substituted with cyano or amino carbonyl;

R^5 is hydrogen or C_{1-4}alkyl;

L is $-X^1-R^6$ or $-X^2-Alk-R^7$ wherein

R^6 and R^7 each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR^5 then R^6 and R^7 may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then R^6 and R^7 may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;

X^1 and X^2 are each independently $-NR^3-$, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or $-S(=O)_2-$;

Alk is C_{1-4}alkanediyl; or

when Y is CR^5 then L may also be selected from C_{1-10}alkyl, C_{3-10}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, or C_{1-10}alkyl substituted with one or two substituents independently selected from C_{3-7}cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, C_{1-6}alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C_{1-6}alkylcarbonyl;

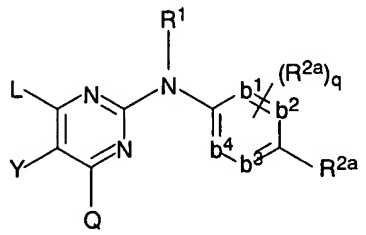
aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro and trifluoromethyl;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl

wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic

heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally he substituted with hydroxy,

or a compound of formula II



(II)

the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

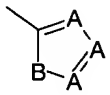
$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);
$-N=CH-C(R^{2a})=CH-CH=$ (b-2);
$-CH=N-C(R^{2a})=CH-CH=$ (b-3);
$-N=CH-C(R^{2a})=N-CH=$ (b-4);
$-N=CH-C(R^{2a})=CH-N=$ (b-5);
$-CH=N-c(R^{2a})=N-CH=$ (b-6);
$-N=N-C(R^{2a})=CH-CH=$ (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)OR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^6;

B is NH, 0, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NH^1-$, -NH-NH-, -N=N-, -0-, -C(=0)-, -CHOH-, -S-, -S(=O)- or $-S(=O)_2-$;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or $-NR^4R^5$; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl

wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}al-

kyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(O)R^6$, $-C(=NH)R^6$, aryl and Het; or

R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}-alkylidene;

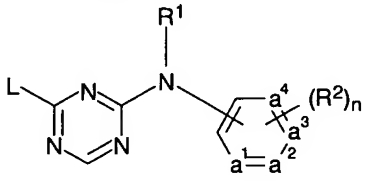
Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^6$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(NH)R^6$ or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical;

said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,

or a compound of formula III



(III)

a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

$-CH=CH-CH=CH-$ (a-1);

-N=CH-CH=CH- (a-2);

-N=CH-N=CH- (a-3);

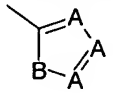
-N=CH-CH=N- (a-4);

-N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;

R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl; and

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=0)R^4$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=0)_pR^4$, $-NH-S(=0)_pR^4$, $-C(=0)R^4$, $-NHC(=O)R$, $-C(=0)NHNH_2$, $NHC(=0)R^4$,$-C(=NH)R^4$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^4;

B is NH, 0, S or NR^4;

p is 1 or 2; and

R^4 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{4-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents

each independently selected from the substituents defined in R^2; or

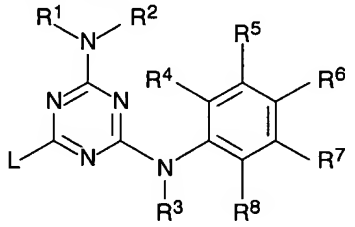
L is $-X-R^3$ wherein

R3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally he substituted with two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy,

or a compound of formula IV



(IV)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R^1 and R^2 are each independently selected from hydrogen; hydroxy; amino; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; Ar^1; mono- or di(C_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyl)aminocarbonyl; dihydro-2(3*H*)-furanone; C_{1-6}alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyc_{1-6}alkyloxy, carboxyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonyl and thienyl; or

R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-6}alkyl)aminoC_{1-4}-alkylidene;

R^3 is hydrogen, Ar^1, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxycarbonyl; and

R^4, R^5, R^6, R^7 and R^8 are each independently selected from hydrogen, hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy;

L is C_{1-10}alkyl, C_{3-10}alkenyl; C_{3-10}alkynyl; C_{3-7}cycloalkyl, or

L is C_{1-10}alkyl substituted with one or two substituents independently selected from C_{3-7}cycloalkyl;

indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C_{1-6}alkylcarbonyl;

phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C_{1-6}alkylcarbonyl; and,

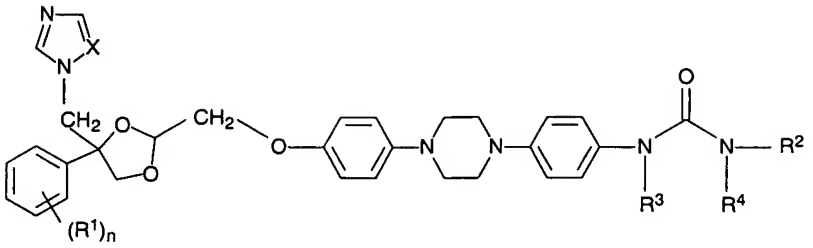
Ar^1 is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro or trifluoromethyl;

with the proviso that compounds (a) to (o)

Co. No.	Alk	R^1/R^2	R^3	R^4	R^5	R^6	R^7	R^8
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH_3	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO_2	H	H
c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C_6H_5	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO_2	H	CH_3	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH_2	H	H
f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF_3	H	H	H
g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	Phenylmethyl	H/H	H	CH_3	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included,

or a compound of formula V



(V)

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof,

wherein

n is zero, 1, 2 or 3;

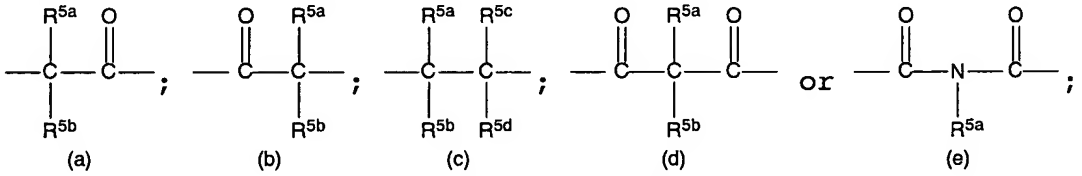
X is N or CH;

each R^1 independently is halo, nitro, cyano, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl;

R^2 is hydrogen; C_{3-7}alkenyl; C_{3-7}alkynyl, aryl; C_{3-7}cycloalkyl; C_{1-6}alkyl or C_{1-6}alkyl substituted with hydroxy, C_{1-4}alkyloxy, C_{3-7}cycloalkyl or aryl;

R^3 and R^4 each independently are hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl; or

R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:

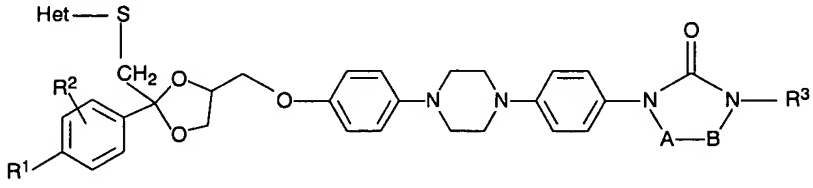


(a) (b) (c) (d) (e)

wherein R^{5a}, R^{5b}, R^{5c}, R^{5d} each independently are hydrogen, C_{1-6}alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl,

or a compound of formula VI



(VI)

the *N*-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula:

-N=CH- (a),
-CH=N- (b),
$-CH_2-CH_2-$ (c),
-CH=CH- (d),
$-C(=O)-CH_2-$ (e),
$-CH_2-C(=O)-$ (f),

in the bivalent radicals- of formula (a) and (h) the hydrogen atom may be replaced by C_{1-6}alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6}alkyl;

R^1 is hydrogen, C_{1-6}alkyl or halo;

R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8}alkyl; C_{3-6}cycloalkyl; or C_{1-8}alkyl substituted with hydroxy, oxo, C_{3-6}cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino or aryl;

pyrimidine; pyrimidine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino or aryl;

tetrazole; tetrazole substituted with C_{1-6}alkyl or aryl;

triazole; triazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino;

thiadiazole; thiadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino;

oxadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino;

imidazole; imidazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino;

thiazole; thiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino;

oxazole; oxazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino;

aryl is phenyl or phenyl substituted with C_{1-6}alkyl or halo, and the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom~~,~~

~~as a solid dispersion in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone~~.

2. (*original*) Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.

3. (*canceled*)

4. (*currently amended*) Particles according to claim ~~3~~ 1, wherein the surfactant is a PEG-n-hydrogenated castor oil.

5. (*previously presented - withdrawn*) Particles according to claim 1, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

6. (*previously presented*) Particles according to claim 1, further comprising citric acid in amounts of up to 5% b.w.

7. (*previously presented*) Particles according to claim 1, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70% b.w. of the total weight of the dosage form.

8. (*original*) Particles according to claim 7, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 50 to 65 % b.w..

9. (*previously presented*) Particles according to claim 1, wherein the controlled release is an instant release of the drug.

10. (*previously presented*) Particles according to claim 1, wherein the controlled release is a sustained release.

11. (*original*) Particles according to claim 10, further comprising hydroxypropyl methyl cellulose in amounts of from 5 to 10 % b.w..

12. (*previously presented*) Particles according to claim 1, obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said mixture and shaping of the extrudate.

13. (*previously presented*) Particles according to claim 1, comprising a compound selected from the group consisting of

4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidyl]amino]benzonitrile;

4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;

4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;

4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidin]amino]-benzonitrile;

4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;

4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-[(2,4,6-trimethylpheny)amino]-1,3,5-triazin-2-yl]-amino]-benzonitrile;

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]-amino]benzonitrile;

4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;

1[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl)-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;

(-)-[2S-[2alpha, 4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxyl]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

14. (*previously presented*) Pharmaceutical dosage form, comprising particles according to a claim 1.

15. (*original*) Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

16. (*new*) Particles according to claim 1, which meet one or both of the following requirements:
    - the surfactant has a HLB-value of from 10 to 18;
    - the surfactant is present in the particles in an amount of from 5 to 20% by weight.

17. (*new*) Particles according to claim 16, wherein the surfactant is a PEG-n-hydrogenated castor oil and/or a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

18. (*new*) Particles according to claim 16, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70% b.w. of the total weight of the dosage form.

19. (*new*) Particles according to claim 18, which meet both of the following requirements:
    - the surfactant has a HLB-value of from 10 to 18;
    - the surfactant is present in the particles in an amount of from 5 to 20% by weight.

20. (*new*) Particles according to claim 1, consisting essentially of the active ingredient,
    from 40 to 70% by weight of the a homo- or copolymer of N-vinylpyrrolidone,
    from 5 to 20% by weight of the surfactant,
    up to 5% by weight of citric acid, and
    up to 25% by weight of hydroxypropyl methyl cellulose.

21. (*new*) Particles according to claim 20, wherein the surfactant has a HLB-value of from 10 to 18.

22. (*new*) Particles according to claim 21, wherein the surfactant is a PEG-n-hydrogenated castor oil and/or a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

23. (*new*) Particles according to claim 1, obtained by a process comprising forming a homogeneous mixture of the components in the form of a melt, extruding said melt and shaping the obtained extrudate.

24. (*new*) Particles according to claim 16, obtained by a process comprising forming a homogeneous mixture of the components in the form of a melt, extruding said melt and shaping the obtained extrudate.

25. (*new*) Particles according to claim 20, obtained by a process comprising forming a homogeneous mixture of the components in the form of a melt, extruding said melt and shaping the obtained extrudate.